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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BRISTOL, LYNN ANNE	

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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,794	GAILONDO COWLEY ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *12-14 and 26-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 15-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-31 are all the pending claims for this application.

2. The amendment to the specification of 10/19/04 to cross-reference the priority documents has been considered and entered.

Election/Restrictions

3. Applicant's election without traverse of Group I (Claims 1-11 and 15-25) in the reply filed on 3/29/07 is acknowledged.

Claims 12-14 and 26-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention of Group II, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/29/07.

4. Claims 1-11 and 15-25 are all the claims under examination.

Priority

5. A certified copy of the Cuban language priority document, CU20020086 (filed 4/29/02), has been received for this application.

Information Disclosure Statement

6. The non-patent literature references cited in the IDS of 1/24/05 have been considered and entered.

Specification

7. The specification is objected to because it does not provide sequence identifiers for the following sequences pursuant to 37 CFR 1.821 (c) and/or (d):

a) (^{20}Phe-Arg^{31})-S-S-(^{87}Ser-Arg^{97}), p. 20, lines 19-20

b) (^{143}Val-Lys^{148})-S-S-(^{186}11e-Lys^{228}), p. 20, line 20

Applicants are required to identify the above-referenced sequences with sequence identifiers in addition to any other sequences that may not be properly identified in the specification and figures.

8. The use of trademarks, e.g., TriPure ™, Lipofectamine PLUS ™ have been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicants are advised to carefully check the entire specification for any trademarks that may not be properly identified.

9. The disclosure is objected to because of the following informalities: the terms "aminoacid" and "aminoacidic" are noted throughout the specification and should be corrected to recite "amino acid".

Appropriate correction is required.

Claim Objections

10. Claims 2, 4 and 6 are objected to because of the following informalities: there appears to be a typographical error for the term "aminoacid" which should recite "amino acid". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-11 and 15-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1, 2, 5 and 7-11 are indefinite for the recitation "of the monomeric scFv type obtained from the RNA extracted from the hybridoma producing Mab CB/ior-CEA.1" in Claim 1, because it is unclear if the monomeric scFv type is expressed as a full protein from an RNA transcript obtained from a recombinant hybridoma or whether the VH and VL domains of the scFv are derived from the RNA encoding the monoclonal antibody comprising the VH and VL domains and produced by the hybridoma.

b) Claims 3, 4, 15, 16, 18, 20, 22 and 24 are indefinite for the recitation "of the divalent (diabody) scFv type obtained from the RNA extracted from the hybridoma producing Mab CB/ior-CEA.1" in Claim 3, because it is unclear if the divalent scFv is expressed as a full protein from an RNA transcript obtained from a recombinant hybridoma or whether the VH and VL domains of the diabody scFv are derived from the

RNA encoding the monoclonal antibody comprising the VH and VL domains and produced by the hybridoma.

c) Claims 1-5, 7-11, 15, 16, 18, 20, 22 and 24 recite the limitation "such antigen" in Claims 1 and 3. There is insufficient antecedent basis for this limitation in the claims. Generic claims 1 and 3 are drawn to human carcinoembryonic antigen (CEA).

d) Claims 1-5, 7-11, 15, 16, 18, 20, 22 and 24 are indefinite for the recitation "dependent on the conservation of *its* glycosylation" in Claims 1 and 3 because it is unclear what "its" is referring to- is glycosylation of CEA, the antibody or both conserved?

e) Claims 6, 17, 19, 21, 23 and 25 are indefinite for the recitation "or fused to biologically or biochemically active domains" in Claim 6 because it unclear what structure is intended by the phrase "active domains". Active domains of what, the VH and VL of SEQ ID NO: 16 or 17?

f) Claims 6, 17, 19, 21, 23 and 25 are indefinite for the recitation "other scFv variants" in Claim 6 because there is no reference to any other scFv or a wild-type scFv to which reference comparison can be made against a scFv variant.

g) Claims 7, 16 and 17 are indefinite for the recitation "in insect or mammalian transfected cells" because it is unclear whether both the insect and mammalian cells are transfected or only mammalian cells.

h) Claims 8, 18 and 19 are indefinite for the recitation "or detectable by other method" because it is unclear what detectable label or agent is contemplated and what other method is being considered in order to detect the label.

i) Claims 11, 24 and 25 are indefinite for the recitation "linked or not to cells" because it is unclear what is intended by the CEA being linked to a cell. Is the CEA membrane associated to a cell and is it also soluble and circulating? How is the CEA "linked or not" to a cell?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit Requirement

12. Claims 1, 3, 5, 7-11, 15, 16, 18, 20, 22 and 24 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

a. It is unclear if a hybridoma cell line which produces an antibody having the exact chemical identity of CB/ior-CEA.1 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. The Examiner's search of the ATCC website and commercial antibody sources did not identify any deposited or commercially available antibody or hybridoma producing such as CB/ior-CEA.1. See attached search output from ATCC (pp.1-3). Without a publicly available deposit of the above cell line, one of

ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species CB/ior-CEA.1. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made

under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit

and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Scope of Enablement

13. Claims 9, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising antibodies derived from CB/ior-CEA.1 Mab, or the monomeric scFv (SEQ ID NO:16), the diabody scFv (SEQ ID NO:17) and fragments thereof, with the intended use of *treating* a CEA-expressing tumor in an art-recognized animal model correlate for a human cancer or tumor, does not reasonably provide enablement for using the same pharmaceutical composition to treat any human with any CEA-expressing tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Relative Skill in the Art

Claim 9 is drawn to a pharmaceutical composition comprising a monomeric scFv derived from Mab CB/ior-CEA.1 and used for treatment of human CEA-expressing tumors. Claim 20 is drawn to a pharmaceutical composition comprising a diabody (dimeric scFv) derived from Mab CB/ior-CEA.1 and used for treatment of human CEA-expressing tumors. Claim 21 is drawn to a pharmaceutical composition comprising CEA antibodies and antibody fragments (i.e., Fab, other scFv variants, bispecific antibodies, or fused to biologically or biochenically active domains) having VH and VL described in SEQ ID NO:16 and 17 and used for treatment of human CEA-expressing tumors.

The relative skill in the art required to practice the invention would be that of an immunopharmacologist/oncologist with expertise in clinical management of cancers using immunotherapeutics.

Disclosure in the Specification

The specification discloses the development and comparison of four CEA antibodies, Mab CB/ior-CEA.1; diabody; scFv and scFv F3 and the affinity constants for

each of the forms are shown in Table VII. On p. 3, line 39- p. 40, line 7, the specification explains that amino acid changes have been introduced into the VH and VL domains from the CB/ior-CEA.1 Mab which improves the affinity constants for both the monomeric (SEQ ID NO:16) and dimeric (SEQ ID NO:17) scFvs of the invention. It is also explained that the scFv F3 embodiment is less effective due to reduced binding as a result of the introduction of amino acid changes into the VH/VL during cloning. The improved monomeric and diabody scFv are described as being smaller in size "that confers these with the potential to better penetrate tissues and to be less immunogenic in the human being, all of which makes them more attractive and presumably superior that the original CB/ior-CEA.1 Mab to direct radioisotopes...to tumors that express human CEA" (p. 4, lines 8-12). Example 9 describes the only in vivo experiment conducted by the Applicants in which any of the inventive antibodies were administered to measure the biodistribution and tumor targeting of the antibodies in a human melanoma (B16-CEA13) bearing mouse. Figure 6 presents the data where "between 24 and 48 hours, the ratio radioactivity in the tumor: radioactivity in blood maintains high for the diabody, the scFv, and the Mab, with the highest values for the latter, followed by the dimeric molecule. The F3 scFv showed very low values..." (p. 25, lines 35-40). Thus in reviewing the contents of the specification, one skilled in the art would not been enabled to have practiced the invention of administering to any human having any CEA-expressing tumor a monomeric scFv, a dimeric scFv much less an CB/ior-CEA.1 (from which the VH and VL for the scFvs was derived) in order to obtain a therapeutic treatment endpoint. The specification does not disclose what treatment endpoints are

contemplated much less how one could treat just any CEA-expressing tumor to obtain a treatment endpoint. In the instant case the claims are not limited by the kind of cancer and a cancer can originate from any number of different cell types (e.g., epithelial, mesothelial or endothelial). Additionally, numerous studies have shown that receptor density and affinity for different therapeutic biomolecules is highly variable amongst different tissues and organs, in addition to there being differences to the extent to which biomolecules are able to penetrate tissues and organs. This suggests that any pharmaceutical composition with an intended administering step as a therapeutic in the realm of a cancer, would require different routes of administration, dosing, formulation, sensitivity of detection, etc., and that one could not predict biodistribution of the therapeutic agent in any subject much less an outcome of success for treating just any CEA-expressing tumor in a human subject in using the same pharmaceutical composition under the same conditions.

Prior Art Status of CB-CEA.1 Antibody Therapy and scFv Immunotherapy/ Undue Experimentation/ Unpredicatbility

In 2006, Perez et al. (Biotechnol. Appl. Biochem. 43:39-48 (2006)) provided a brief overview of anti-CEA antibody therapeutic candidates as potentially useful for radioimmunotherapy and for specific delivery of anti-tumor toxins, drugs and other bioactive materials. Perez described a new generation of recombinant CEA antibodies which had already advanced to clinical trials: "a) CEA-Cide® (labetuzumab) naked/radiolabelled humanized antibody from Immunomedics (Phase I/II clinical trials for treatment of solid tumors, b) the chimeric and minibody versions of antibody T84.66

(chT84.66) reported in Phase I in patients with metastatic CEA-producing malignancies and in human pilot trials (citing Wong et al. Clin. Can Res. 6:3855-3863 (2000); Wong et al. Clin. Can. Res. 9:5842-5852 (2003); Wong et al. Clin. Can. Res. 10:5014-5021 (2004)), respectively, and c) MFE-23, an scFv (single-chain Fv) antibody fragment selected from phage display that has been shown to successfully localize tumor deposits in humans (citing Begent et al. Nat. Med. 2:979-984 (1996); Mayer et al. Clin. Can. Res. 6:1711-1719 (2000))" (p. 39, Col. 1). Perez also mentioned the clinical trials of Oliva et al. where a ^{99m}Tc-labeled version of CB/ior-CEA.1 Mab was approved for diagnosis and follow-up of human colorectal tumors in Cuba and other countries (p. 39, Col. 2, ¶2). Perez describe the criticality in maintaining the consensus or original sequences from the VH and VL of the parent CB/ior-CEA.1 Mab in constructing what is the instant claimed diabody scFv (discussed at p. 40, Col. 1, ¶1; p. 44. Col. 1, ¶2; and p. 46, Col. 2, ¶2).

Notably, Perez actually teaches away from using monomeric scFv derived from CB/ior-CEA.1:

"Multivalent fragments have been reported to offer advantages over univalent scFv for tumor imaging, RIT and drug targeting. The major gain in functional binding affinity (avidity) towards the target antigen is produced due to the reduced association rate resulting from multiple binding of two (or more in the case of multivalence) surface antigens, and a consequent higher probability of rebinding (tumor retention). At the same time, multivalent constructs maintain important features of scFv, including small

sizes that allow more effective and homogeneous tumor penetration and potentially reduced immunogenicity" (p.44, Col. 1).

In general, the field of art recognizes scFv and multimeric scFvs (diabodies) as the next generation of Ab-based molecules in treatment of solid tumors. Beckman et al. Can. 109:170-179 (2007)) discuss the relevance of achieving a) tumor penetration and retention and b) favorable plasma pharmacokinetics in promoting tumor exposure. "Studies in tumor-bearing rodents are often confounded by lack of normal tissue reactivity with Ab constructs directed toward human Ags, but studies in transgenic animals can be performed in some instances to alleviate this issue. For example, CEA-transgenic mice were used to test anti-CEA mAbs and revealed specific accumulation in normal gastrointestinal mucosa as well as in adenomas and tumors...Theoretical models may help to understand and interpret experimental results, to prioritize further experimental work, and to translate experiments in murine systems to humans" (p. 175, Col. 2, ¶5 to p. 176, Col. 1, ¶1). Finally, "In optimizing Ag-Ab constructs for affinity and other properties it is well to bear in mind the mechanism of cell kill, and the requirements in terms of percent occupancy and long residence time are required for cell kill, high affinity may be preferable and the approach would have to be to treat the outer layer of the tumor with each course. Tumors are genetically unstable, however, and if antibody therapies take too long to penetrate them, may acquire resistance" (p. 176, Col. 1, ¶2).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry

standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar. One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not correlate with results expected in human CEA-expressing tumors.

Thus based on the specification and the Perez disclosure, one skilled in the art could not have practiced treating any human CEA-expressing tumor with a pharmaceutically-formulated monomeric CEA scFv, dimeric CEA scFv or antibody fragments containing the VH/VL of the parent CB/ior-CEA.1 antibody for targeted delivery of the molecule as an intended therapeutic. The lack of in vivo animal model testing for any of the instant claimed embodiments in the instant specification and for CB/ior-CEA.1 antibodies in general, and the limited clinical trial successes demonstrated with full length chimeric or humanized CEA antibodies in diagnostic applications do not allow one of skill in the art to predict or extrapolate which of any of the embodiments could be pharmaceutically formulated to treat just any human CEA-expressing tumors of any kind. The significant lack of in vivo testing would require that

one of skill in the art perform trial and error experimentation for the different CEA antibody embodiments on different human tumor cell lines in vitro that could also be used in xenograft experiments (or transgenic animal models) in "to be determined" appropriate mouse strain(s) and which are art-recognized animal model correlates for human CEA-expressing tumors. Thus on the basis of the specification and the prior art references of Perez, Beckman and Dennis, the instant pharmaceutical compositions were not enabled for the scope of the invention as presently claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1, 3, 5-8, 10, 11, 15-19, and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tormo et al. (APMIS 97(12):1073-80 (1989); cited in the 892 form of 3/6/07' Abstract) in view of Freyre et al. (J. Biotechnol. 76:157-163 (2000))

as evidenced by Ayala et al. (Conf. On Plant-Made Pharmaceuticals 2005; Abstract) and further in view of Hollinger et al. (PNAS 90:6444-6448 (1993); cited in the IDS of 1/24/05 and the 892 form of 3/6/07).

Claims 1, 5, 7, 8, 10 and 11 are drawn to monomeric scFv derived from CB/ior-CEA.1 Mab producing hybridoma. Claims 3, 15, 16, 18, 22 and 24 are drawn to divalent (diabody) scFv derived from CB/ior-CEA.1 Mab producing hybridoma. Claims 6, 17, 19, 23 and 25 are drawn to recombinant or synthetic antibodies comprising the VH and VL domains from SEQ ID NOS: 16 and 17, and which correspond to the VH and VL domains of the parent CB/ior-CEA.1 Mab producing hybridoma.

The instant claimed monomeric scFv, diabody scFv, recombinant antibody fragments comprising the VH and VL of the parent CB/ior-CEA.1 antibody were obvious at the time of the invention in view of Tormo and Hollinger as evidenced by Ayala.

Tormo discloses the instant hybridoma and CB/ior-CEA.1 murine Mab as being highly specific for human CEA with no cross-reaction with CEA-related molecules that shows no recognition of normal tissues, except for cells of the normal colon epithelium with polarized CEA expression.an anti-CEA (CB-CEA-1). Tormo does not disclose Ab constructs such a monomeric and diabody scFvs using the VH and VL domains from the parent antibody. Freyre as evidenced by Ayala and Hollinger rectifies this deficiency in its disclosure.

The scFv produced by Freyre et al. in 2000 using the VH and VL of CB/ior-CEA.1 was producible at high levels but significantly reduced in antigen binding because numerous changes had been introduced into the VH/VL domains during cloning as

evidenced by Ayala, thus Hollinger provided an alternative means for producing scFv forms by maintaining the integrity of the original VH and VL domain sequences of the parent antibody.

Hollinger discloses recombinant antibody fragments using variable domains encoded by genes from mouse hybridomas to make constructs for expressing scFv, bivalent and bispecific antibody fragments that have the advantages of retaining the antigen recognition of the parent antibody, being small in size, assembled in vivo and harvested directly from culture supernatant.

One skilled in the art would have been motivated to have combined the techniques of Tormo and Hollinger as evidenced by Ayala to obtain an improved antibody fragment having at least the binding properties of the parent CB/ior-CEA.1 antibody and the advantages of being readily producible as a properly assembled and secreted antibody fragment by transfected cells in vitro or in vivo and been reasonably assured of success in doing so based on the disclosures of Tomoro, Freyre as evidenced by Ayala and Hollinger. The Tormo CEA antibody was highly selective and non-crossreactive for purposes of using such an antibody in targeted diagnostics or therapeutics for CEA-expressing tumors, and because obtaining smaller sized Ab fragments was more desirable for retaining antigen binding and for tumor penetration, one skilled in the art would have been motivated to have obtained scFv from the CB/ior-CEA.1 parent antibody based on Freyre, and because Freyre's scFv was already established at the time of the invention to be reduced in its affinity compared with the parent Ab as evidenced by Ayala, one would have been further motivated to have

obtained an scFv or diabody which possessed reproducible or approximate binding properties to the parent Mab based on the disclosure of Hollinger. Taken together, one skilled in the art would have been reasonable assured of success in producing the instant claimed CEA antibody embodiments based on the disclosures of Tormo, Freyre as evidenced by Ayala and Hollinger because all the materials and reagents were available for producing recombinant CEA Abs, and Freyre had established the importance of VH and VL sequence fidelity in generating a scFv with high affinity binding and Hollinger provided an alternative method to for cloning VH and VL domains from a parent Mab into a scFv or diabody structure in order to produce a smaller sized but high affinity antibody variant of the parental Mab.

For all of these reasons, the claims were prima facie obvious at the time of the invention over Tormo, Freyer as evidenced by Ayala and Hollinger.

Conclusion

15. No claims are allowed.

16. The search of commercial protein sequence databases against SEQ ID NO:16 and 17 did not reveal any other sequences having 100% identity or homology with either of the claimed sequences.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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